PATENT SPECIFICATION

NO DRAWINGS

847,205

Date of Application and filing Complete Specification: Oct. 22, 1958.

No. 33785/58.

Application made in Switzerland on Oct. 25, 1957.

Application made in Switzerland on April 26, 1958.

Complete Specification Published: Sept. 7, 1960.

Index at acceptance:—Class 2(3), C1F2(C2:D1), C2B(29:43A4), C3A10A(4G:5A2:5K), C3A10E(3D1:5A:5E).

International Classification:—C07d.

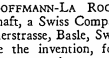
COMPLETE SPECIFICATION

# A process for the Manufacture of Ethylenimine Derivatives and Novel Ethylenimine Derivatives

We, F. HOFFMANN-LA ROCHE & Co., Aktiengesellschaft, a Swiss Company of 124—184, Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel ethylenimine derivatives and with a process for the manufacture thereof.

The novel ethylenimine derivatives provided by the invention are compounds of the general formula:



wherein $R^1$ stands for a hydrogen atom or for an alkyl, *cyclo*alkyl, aryl or aralkyl group and $R^2$ stands for the carboxyl or aminocarbonyl group or, when $R^1$ stands for other than a hydrogen atom, for an alkoxycarbonyl group, and acid addition salts thereof. These substances and the partly known 2-alkoxycarbonyl-ethylenimine compounds (and acid addition salts thereof) are useful as intermediates for the preparation of α-amino-β-hydroxy-carboxylic acids and esters thereof (e.g. serine or serine methyl esters), α-amino-β-chlorocarboxylic acids and esters thereof (e.g. *iso*propyl α-amino-β-chloro-propionate) 4-amino-*iso*-oxazolidone-(3) as well as 5-substituted derivatives thereof.

Typical radicals represented by $R^1$ in the foregoing formula include such alkyl groups containing up to four carbon atoms (e.g. methyl, ethyl, propyl, *iso*propyl and butyl), higher homologous alkyl groups such as octyl and nonyl, *cyclo*alkyl groups such as *cyclo*pentyl and *cyclo*hexyl, monocyclic aryl groups such as phenyl and *p*-nitrophenyl and aralkyl groups such as benzyl. Preferred groups represented by $R^2$ are alkoxycarbonyl groups containing up to four carbon atoms in the alkoxy portion, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, *iso*propoxycarbonyl and butoxycarbonyl.

According to the process provided by the invention, the novel substances aforesaid and 2-alkoxycarbonyl-ethylenimines and acid addition salts thereof are manufactured by reacting a bromo compound of the general formula:

or

(wherein $R^1$ and $R^2$ have the previously given significance, except that $R^2$ may also represent an alkoxycarbonyl group when $R^1$ represents a hydrogen atom) with liquid ammonia and, if desired, converting the resulting ethylenimine compound into an acid addition salt thereof.

The preferred monobromo starting materials for the process are alkyl esters containing up to four carbon atoms in the characterizing alkyl group of the ester radical, especially the methyl, ethyl and *iso*propyl esters of α-bromo-acrylic acid, α-bromo-crotonic acid, 2-bromo-decen-(2,3-oic-(1) acid, 2-bromo-undecen-(2,3)-oic-(1) acid, α-bromo-β-phenyl acrylic acid and α-bromo-β-(*p*-nitro-phenyl)-acrylic acid, but those in which $R^2$ is the carboxyl or aminocarbonyl group are also useful.

The preferred dibromo starting materials are alkyl esters containing up to four carbon atoms in the characterizing alkyl group of the ester radical, especially the methyl, ethyl and *iso*propyl esters of α,β-dibromo-propionic acid or α,β-dibromo-butyric acid, and they are easily accessible.

When treated with liquid ammonia, the $\alpha,\beta$-dibromo compounds used as starting materials are first converted into the corresponding monobromo compounds (see formulae). As the reaction continues, the monobromo compounds are converted into the compounds of the formula first written.

If the symbol $R^2$ in the formula of the starting material stands for a methoxycarbonyl group, the main reaction product is the acid amide. In the case of the higher homologous esters (such as the ethyl, *iso*propyl or butyl esters) however the ester group generally remains unchanged in the reaction.

The ethylenimine compounds obtained in the process form acid addition salts by reaction with inorganic or organic acids such as the mineral acids (e.g. hydrochloric acid, hydrobromic acid, hydriodic acid, sulphuric acid or phosphoric acid) or oxalic acid, aryl-sulphonic acids (e.g. benzenesulphonic acid or *p*-toluenesulphonic acid).

In order to prevent polymerization, polymerization inhibitors such as hydroquinone, *p*-phenylene-diamine, diphenyl amine or phenyl-*beta*naphthylamine may be added during the reaction. The liquid ammonia used in the reaction may contain some water.

In order that the process of the invention may be more clearly understood and readily carried into effect, examples will now be given:

EXAMPLE 1

28 g of ethyl α-bromo-acrylate was dropped into 500 ml of liquid ammonia and stirred for 4 hours. The mixture was evaporated to dryness and the residue was extracted with 500 ml of acetonitrile, the ammonium bromide formed remaining undissolved. The filtrate was evaporated and extracted with 400 ml of absolute ether. A small amount of a resinous residue remained. The filtrate was concentrated. The residue was a red oil containing colourless 2-ethoxycarbonyl-ethylenimine; b.p. = 53°—54°C/11 mm, $n_D^{23.5} = 1.4372$, $d^{20} = 1.0592$.

A solution of 1 g of picric acid in 20 ml of ethanol was added to a solution of 0.5 g of 2-ethoxycarbonyl-ethylenimine in 1 ml of ethanol. The 2-ethoxycarbonyl-ethylenimine picrate crystallized out of the concentrated reaction mixture; m.p. = 90°—91°C.

4.6 g of 2-ethoxycarbonyl-ethylenimine was slowly added to 10 ml of 38% hydrochloric acid at 0°C and stirred for 15 minutes. The mixture was poured into 20 ml of ethanol and evaporated to dryness at 30°C. The oily residue was then repeatedly dissolved in ethanol and again dried *in vacuo*. The residue was now further dried in a high vacuum over sodium hydroxide, whereby the oil solidified. It consisted of 38% of *iso*chloro-serine ethyl ester hydrochloride, as determined by titration according to CHROMWELL (J. Am. Chem. Soc. 1948, *70*, 1320) and of 62% of chloro-serine ethyl ester hydrochloride.

EXAMPLE 2

78 g of ethyl $\alpha,\beta$-dibromo-propionate was dropped into 200 to 300 ml of liquid ammonia and stirred for 2 hours. The product was worked up according to the procedure of Example 1, whereupon pure 2-ethoxycarbonyl-ethylenimine was obtained.

EXAMPLE 3

26 g of ethyl $\alpha,\beta$-dibromo-propionate was dissolved in 200 ml of liquid ammonia and stirred for 3 hours. After separating the ammonia, the residue was directly distilled in a high vacuum. The distillate containing 2-ethoxycarbonyl-ethylenimine was condensed in a dry ice trap.

EXAMPLE 4

78 g of ethyl $\alpha,\beta$-dibromo-propionate was dissolved in one litre of liquid ammonia and stirred for 40 minutes. The mixture was then concentrated and treated with 50 ml of water in order to completely dissolve the residue. The solution was saturated with sodium chloride and extracted four times with 400 ml of ether. The extract was dried with sodium sulphate and the filtrate was evaporated at 20°C/12 mm. There was obtained an oily residue which, after distillation, yielded 2-ethoxycarbonyl-ethylenimine.

EXAMPLE 5

74 g of methyl $\alpha,\beta$-dibromo-propionate was dissolved in 1.2 litres of liquid ammonia and stirred for 40 minutes. The mixture was then concentrated and the residue extracted with 600 ml of acetonitrile. There remained a residue which consisted primarily of ammonium bromide. The filtrate was evaporated, the residue was extracted with methylene chloride, the filtrate was again evaporated and the residue again extracted with ether. After evaporating the ether solution there remained a light easily flowing oil, which, after a third distillation at 50°—65°C/11 mm. yielded 2-methoxycarbonyl-ethylenimine; $n_D^{24} = 1.4390$, $d^{20} = 1.1181$.

From the residue of the ether extraction there was isolated the amide of 2-carboxy-ethylenimine. Upon recrystallization from ethanol/ether, it melted at 116°—118°C.

EXAMPLE 6

40 g of butyl $\alpha,\beta$-dibromo-propionate was stirred for 4 hours in 500 ml of liquid ammonia. After evaporation, the residue was extracted with acetonitrile and the residue, consisting of ammonium bromide, was separated by filtration. The filtrate was evaporated and extracted with ether. The ethereal solution was evaporated and the residual oil was distilled in vacuo at 83°—84°C/13 mm to obtain 2-butoxycarbonyl-ethylenimine; $n_D^{25} = 1.4400$.

EXAMPLE 7

82.2 g of ethyl $\alpha,\beta$-dibromo-butyrate was stirred for 0.5 hours in 900 ml of liquid ammonia. After evaporation, the residue was extracted with 700 ml of acetonitrile. The ammonium bromide residue was filtered off

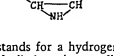
and the filtrate was evaporated. The residue was extracted with 500 ml of ether. The ethereal solution was filtered and evaporated, leaving an oily residue. This yielded upon distillation at 70°—75°C/12 mm 2-methyl-3-ethoxycarbonyl-ethylenimine; $n_D^{24} = 1.4404$.

EXAMPLE 8

82 g of isopropyl $\alpha,\beta$-dibromo-propionate was introduced dropwise within 1.25 hours into 1200 ml of liquid ammonia which contained as stabilizer 0.8 g of phenyl-*beta*-naphthylamine. The mixture was further stirred for 3 hours and then the ammonia evaporated *in vacuo*. The solid residue was taken up in 500 ml of ether and 200 ml of a saturated sodium chloride solution. The ethereal phase was separated and the aqueous solution extracted with two portions of 500 ml of ether. The combined ethereal extracts were dried with sodium sulphate and, after filtration, evaporated *in vacuo*. The oily residue yielded upon distillation at 52°—53°C/11 mm 2-*iso*propoxycarbonyl-ethylenimine.

WHAT WE CLAIM IS:—

1) Ethylenimine derivatives of the general formula:



wherein $R^1$ stands for a hydrogen atom or for an alkyl, *cyclo*alkyl, aryl or aralkyl group and $R^2$ stands for the carboxyl or aminocarbonyl group or, when $R^1$ stands for other than a hydrogen atom, for an alkoxycarbonyl group, and acid addition salts thereof.

2) Substances as claimed in claim 1, wherein the group $R^2$ is an alkoxycarbonyl group containing up to four carbon atoms in the alkoxy portion and the group $R^1$ is an alkyl group containing up to four carbon atoms.

3) 2-methyl-3-ethoxycarbonyl-ethylenimine.

4) A process for the manufacture of the substances claimed in claim 1 hereof and 2-alkoxycarbonyl-ethylenimines and acid addition salts thereof, which process comprises reacting a bromo compound of the general formula:

or

(wherein $R^1$ and $R^2$ have the significance as given in claim 1, except that $R^2$ may also represent an alkoxycarbonyl group when $R^1$ represents a hydrogen atom) with liquid ammonia and, if desired, converting the resulting ethylenimine compound into an acid addition salt thereof.

5) A process in accordance with claim 4, wherein the group $R^2$ in the starting material is an alkoxycarbonyl group containing up to four carbon atoms in the alkoxy portion and the group $R^1$ is an alkyl group containing up to four carbon atoms.

6) A process as claimed in claim 4 or claim 5 as the case may be, wherein ethyl or *iso*propyl $\alpha$-bromo-acrylate or methyl, ethyl or *iso*propyl $\alpha,\beta$-dibromo-propionate or ethyl or *iso*propyl $\alpha,\beta$-dibromo-butyrate is used as the starting material.

7) A process in accordance with claim 4, 5 or 6, wherein a polymerisation inhibitor is included with the reactants.

8) A process for the manufacture of the substances claimed in claim 1 hereof and 2-alkoxycarbonyl-ethylenimines and acid addition salts thereof, substantially as described with reference to the examples given.

W. D. WHITAKER,
Patent Agent,
For: F. HOFFMANN LA-ROCHE & CO.,
Aktiengesellschaft.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1960.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.